

The University of Chicago

STUDIES IN THE MATHEMATICAL BIOPHYSICS OF CELL DIVISION

A DISSERTATION SUBMITTED TO THE
FACULTY OF THE DIVISION OF THE
BIOLOGICAL SCIENCES IN CANDIDACY FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF PHYSIOLOGY
(MATHEMATICAL BIOPHYSICS)

1941

By

HERBERT DANIEL LANDAHL

Reprinted from

THE BULLETIN OF MATHEMATICAL BIOPHYSICS, Vol. 4, No. 1, March, 1942;
No. 2, June, 1942; No. 3, September, 1942; No. 4, December, 1942

Introduction Privately Printed

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INTRODUCTION

The nature of the phenomena associated with the process of cell division is in the most part obscure in spite of the wealth of observations from normal and experimental conditions. The complexity of the phenomena is brought out in the many observations. Among the many questions that arise is that concerning the forces involved in the various deformations and movements associated with division of cells. In particular we shall interest ourselves only in the problems arising from deformations of the cell as a whole, omitting the problems arising in connection with the movements and deformations of constituent parts.

Even with these restrictions the problem can hardly be handled in its full complexity. Thus, one may attempt to abstract from the actual complex phenomena certain essential elements, remaining quite aware that others are omitted. Having these elements and the relationships among them, one may attempt to predict the course of certain events. If all the major elements were accounted for, and the necessary inter-relationships known, then the events would be predicted, provided the logical deductions could be carried out. If the inter-relationships are stated in mathematical terms, the deductions can be made if the resulting equations can be solved. In this case, agreement between theory and experiment to a certain degree of approximation necessarily follows, since this is what is meant by taking the necessary factors into account.

Unfortunately, one does not know all the important elements involved in the particular part of the problem of cell division to which we limit our discussion, nor does one know all the necessary inter-relationships among the elements. This does not prevent one from considering the theoretical problems arising when one assumes certain factors to be acting and, where necessary, introduces arbitrary expressions for the inter-relationships among these factors. If very few assumptions have had to be made, and one does find that the predicted results agree with those observed, one is justified in concluding that the agreement may be more than accidental, and that further predictions involving no further assumptions, may be expected to hold. When predictions are found to be correct, one's confidence in the original assumptions is increased.

In a complex situation, as that before us, very few deductions can be made unless the various relationships among elements can be set down in analytic form and the resulting equations treated mathematically. In fact, most of the problems are such that one has to resort to approximate solutions. In many instances, this may not be a handicap.

One of the forces which may be involved is the gross deformations accompanying cell division is that of the drag on granules and particles in the cell due to the continuous flow of metabolites. The effect of these forces can be observed under special conditions, though with considerable difficulty. One problem then arises as to the magnitude and direction of these forces. This problem has been treated in several papers, but certain assumptions were made which did not correspond to the real situation. Thus, in the next section we shall consider this problem from more general grounds.

A differential equation has been developed by N. Rashevsky for the rate of elongation of a cell in which there is a net outward force due to diffusion drag, and which is under the influence of surface tension, osmotic forces and viscosity. Similar expressions are obtained under somewhat more general assumptions and the sensitivity of the form of the expression to certain factors is considered. An integrated expression for the elongation with time is derived by an approximation method. Measurements of a number of eggs during division, from photographs made by Dr. R. Buchsbaum and R. R. Williamson, are compared with the theoretical expectations and the parameters are evaluated.

Similarly, an equation, derived by G. Young, for the rate of constriction, is compared with measurements and the parameters of the equation are evaluated. One of the parameters is the same in the two equations. The fact that this parameter turns out to be of the same order of magnitude in the two cases is very significant.

Among the forces involved in deformations of the cell are those of surface tension and membrane forces. For this reason, the effect of those forces, when acting alone, is considered. An expression is derived for change of shape with time, when the cell remains approximately an oblate or prolate ellipsoid of revolution. The equations are compared with experimental data available and the significance of the agreement is discussed.

The shape of a freely elongating cell may give some suggestions as to the nature of the underlying processes. An approach to this problem is discussed in the last section as well as the significance of certain relations obtained from measurements of the cells.

A KINETIC THEORY OF DIFFUSION FORCES IN METABOLIZING SYSTEMS

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The development of a molecular theory of the diffusion drag forces in liquids is attempted by considering the liquids as limiting cases of very dense gases. An expression is derived for the force on a small particle suspended in a nonuniform mixture of such gases on the basis of kinetic theory. Another expression for the order of magnitude of the force on a larger particle is obtained by introducing certain hydrodynamical considerations. These results are compared with an expression previously derived by N. Rashevsky, and estimates are made of the order of magnitude of the volume force on the granules and particles within a typical cell due to the diffusion of metabolites. It is found that the drag forces, exerted by a diffusing solute, depend to a very large extent on the physical properties of the solvent.

The drag forces exerted by a diffusing substance must be considered in a complete theory of metabolizing systems. It has been suggested that they may play an important role in cell division and other phenomena (Rashevsky, 1938). An expression for the force on a particle due to a diffusing substance was derived by N. Rashevsky on the basis of asymmetric molecular bombardments. A corresponding expression was derived by G. Young (1938) on the basis of a hydrodynamical treatment. In the former treatment the effect of the solvent was not adequately accounted for, while in the latter, it was neglected. It is the purpose here to derive a more complete expression on the basis of the kinetic theory of gases.

We shall consider the solvent and solute as non-uniform dense gases diffusing through each other in the presence of another kind of solute molecules, having only thermal motion. If the stationary solute is sufficiently dilute, interactions between these molecules may be neglected, and we may consider the force on each molecule separately. Thus for convenience we shall consider only one such molecule, and, in order to distinguish it from the other molecules we shall refer to it as the particle. The molecules of the solvent will be referred to as class 1, and the parameters for these molecules will bear the subscript 1. Similarly the solute molecules will be referred to as class 2, while the subscript 3 will refer to the particle.

Let N_1 be the molecular density of molecules 1 of mass m_1 and

diameter σ_1 , for which the most probable thermal speed is $\alpha_1 = \sqrt{2kT/m_1}$. A similar notation will be used for molecules of class 2, and for the particle, except that N is not defined for the particle. Let $\mathbf{c}_i$ be the velocity of a particular member of class i before, and $\mathbf{c}'_i$ the velocity after collision. The molecules of all classes are assumed to be elastic spheres.

Since we intend to extrapolate any results to liquids, we wish to consider the effects due to the finite sizes of the molecules. The first approximation, f_1^0 , to the distribution function of the velocities of class 1 molecules, f_1 , is given by the Maxwell distribution. An equation, whose solution gives a second approximation to $f_1 = f_1^0 + f_1^1$ for a mixture of two dense gases, is given by S. Chapman and T. G. Cowling (1939). Similarly, equations for collision frequency are given, so that one may obtain the average change in velocity of the particle. The presence of a third type of particle introduces a further complication. We shall not attempt this general type of approach, but use a procedure in which the effect of molecular size will be considered in connection with collision frequency, but neglected in connection with the second approximation to the distribution function, f_1 . The effect of the size of the particle on the distribution function will be similarly neglected. If only the particle size were to be considered, one might treat its effect on the distribution function as done by P. C. Epstein (1924) in obtaining Stoke's law. The distribution functions will be considered as independent of position and the effect of position will be brought in as is frequently done in this type of problem.

The number of molecules per unit volume having velocities in the element, $d\mathbf{c}$, of velocity space, is $Nf d\mathbf{c}$. Then f_1 , the distribution function for a class 1 molecule, is given by

$$f_1 = \pi^{-3/2} \alpha_1^{-3} e^{-\frac{(\mathbf{c}_1 - \omega)^2}{\alpha_1^2}}, \quad (1)$$

where ω is the mass velocity of the mixture. A similar expression holds for class 2 molecules. For the particle we have

$$f_3 = \pi^{-3/2} \alpha_3^{-3} e^{-\frac{c_3^2}{\alpha_3^2}}, \quad (2)$$

as we consider the particles to have only thermal motion.

Consider a collision between a molecule of class 1 and the particle. Let $\mathbf{k}$ be a unit vector from the center of the particle through the center of the molecule 1. The change in velocity of the particle is given by the expression (Chapman and Cowling, 1939, p. 58)

$$\mathbf{c}'_3 - \mathbf{c}_3 = -\frac{2m_1}{m_1 + m_3} (\mathbf{c}_{31} \cdot \mathbf{k}) \mathbf{k}, \quad (3)$$

$$\mathbf{c}_{31} = \mathbf{c}_3 - \mathbf{c}_1 = -\mathbf{c}_{13}. \quad (4)$$

If dk represents an element of surface on a sphere of unit radius containing the point $\mathbf{k}$, then the probable number of collisions per second of molecules of velocity $\mathbf{c}_1$ with the particle, such that $\mathbf{k}$ lies in the range dk , is given by

$$\chi_{31} N_1 \sigma_{31}^2 (\mathbf{c}_{31} \cdot \mathbf{k}) dk, \quad (5)$$

$$\sigma_{31} = (\sigma_3 + \sigma_1)/2, \quad (6)$$

where χ_{31} is a factor depending on the density of the particles, its value being unity for rarified gases (Chapman and Cowling, 1939, p. 292), and where N_1 is evaluated at the position of molecule 1 at its last collision with any molecule of either class 1 or 2. The net acceleration of the particle is the average change in velocity per unit time, or the integral of the expression obtained by multiplying the factors from (1), (2), (3) and (5). Multiplying the acceleration by the mass, m_3 , we obtain $\mathbf{F}_{31}$ as the force on the particle due to bombardments of class 1 molecules where

$$\mathbf{F}_{31} = -\frac{2m_1 m_3 \sigma_{31}^2}{m_1 + m_3} \iiint \chi_{31} N_1 (\mathbf{c}_{31} \cdot \mathbf{k})^2 f_1 f_3 \mathbf{k} dk d\mathbf{c}_1 d\mathbf{c}_3. \quad (7)$$

The value of N_1 is given by

$$N_1 = N_{10} + (\sigma_{31} \mathbf{k} - L_{12} \mathbf{c}_1 / c_1) \cdot \text{grad } N_{10}, \quad (8)$$

since N_1 is taken at the point of last collision. The quantity L_{12} is the mean free path of molecule 1 in the mixture of 1 and 2 molecules. We shall use the expression corrected for persistence of velocity (Jeans, 1940, p. 206) in which the χ factors have been introduced and in which the coefficient α_{12} is taken equal to 0.2 and $\theta = 0.4$. Then

$$L_{12} = \frac{\sqrt{m_1 + m_2}}{1.2 \pi \sigma_{12}^2 N_{20} \chi_{12} \sqrt{m_2} + .6 \sqrt{2} \pi \sigma_1^2 N_{10} \chi_{11} \sqrt{m_1 + m_2}}. \quad (9)$$

The values N_{10} and N_{20} are the values which N_1 and N_2 would take at the center of the particle if the latter were absent. Expressions similar to (6), (7), (8) and (9) may be obtained for collisions of molecules of class 2 with the particle by interchanging the subscripts 1 and 2.

The factor χ_{31} depends upon the number densities N_1 and N_2 in general, and upon σ_1 and σ_2 as well as upon σ_3 . To a first approximation we may write

$$\chi_{31} = \chi_3 + a_1 N_1 + b_1 N_2. \quad (10)$$

The value of χ_3 is unity if the effect of the particle is neglected, otherwise it is greater than one. The factor χ_{31} is to be evaluated at $\frac{1}{2}\sigma_{13}\mathbf{k}$, the point between centers at collision.

Introducing (1), (2) and (8) into (7), and defining ν_1 as a unit vector in the direction of the gradient of N_1 , we obtain for the expression under the integral, where $\omega = \omega_1 \nu_1$:

$$\begin{aligned}
 & \frac{N_1 \chi_{31}}{\pi^3 \alpha_1^3 \alpha_3^3} \iiint e^{-\frac{c_1^2}{a_1^2}} e^{-\frac{c_3^2}{a_3^2}} (\mathbf{c}_{31} \cdot \mathbf{k})^2 \mathbf{k} d\mathbf{k} d\mathbf{c}_1 d\mathbf{c}_3 + \frac{2N_1 \omega_1 \chi_{31}}{\pi^3 \alpha_1^5 \alpha_3^3} \\
 & \quad \times \iiint e^{-\frac{c_1^2}{a_1^2}} e^{-\frac{c_3^2}{a_3^2}} (\mathbf{c}_1 \cdot \nu_1) (\mathbf{c}_{31} \cdot \mathbf{k})^2 \mathbf{k} d\mathbf{k} d\mathbf{c}_1 d\mathbf{c}_3 \\
 & + \frac{(\chi_{31} + .5a_1 N_1 - 5b_1 N_1)}{\pi^3 \alpha_1^3 \alpha_3^3} \sigma_{31} \frac{\partial N_1}{\partial \nu_1} \iiint e^{-\frac{c_1^2}{a_1^2}} e^{-\frac{c_3^2}{a_3^2}} \\
 & \quad (\mathbf{k} \cdot \nu_1) (\mathbf{c}_{31} \cdot \mathbf{k})^2 \mathbf{k} d\mathbf{k} d\mathbf{c}_1 d\mathbf{c}_3 - \frac{\chi_{31} L_{12}}{\pi^3 \alpha_1^3 \alpha_3^3} \frac{\partial N_1}{\partial \nu_1} \\
 & \quad \times \iiint e^{-\frac{c_1^2}{a_1^2}} e^{-\frac{c_3^2}{a_3^2}} \frac{(\mathbf{c}_1 \cdot \nu_1)}{c_1} (\mathbf{c}_{31} \cdot \mathbf{k})^2 \mathbf{k} d\mathbf{k} d\mathbf{c}_1 d\mathbf{c}_3.
 \end{aligned} \tag{11}$$

In the above expression only terms in the first power of the gradient of N_1 are retained. The mass velocity is considered due only to diffusion and hence is proportional to $\partial N_1 / \partial \nu_1 = \partial N_2 / \partial \nu_2$. For it we shall use the expression given by Loeb (1934, p. 263), using somewhat different notations, but in which L_{12} is given by (9) above:

$$\omega_1 = \frac{2}{3\sqrt{\pi}(N_1 + N_2)} (\sigma_1 L_{12} - \sigma_2 L_{21}) \frac{\partial N_1}{\partial \nu_1}. \tag{12}$$

The second term arises from the first term of the expansion of (1), since $\omega_1 \ll \alpha_1$. The subscript o has been dropped so that χ_{31} , N_1 and N_2 hereafter are to be taken at the center of the particle.

From consideration of symmetry, we can see that the net force must lie in the direction of the gradient. Thus $\mathbf{F}_{31} \cdot \nu_1$ is the value desired and the force is then with reference to the direction ν_1 . We thus take the component of each term of (11) in the direction ν_1 . The integration with respect to $d\mathbf{k}$ may be simplified by the substitutions:

$$l = (\mathbf{k} \cdot \mathbf{c}_{31}) / c_{31}, \cos \beta = (\mathbf{c}_{31} \cdot \nu_1) / c_{31}, m = \mathbf{k} \cdot \mathbf{q},$$

where

$$\begin{aligned}
 \mathbf{q} &= \csc \beta (\nu_1 - \cos \beta \mathbf{c}_{31} / c_{31}), d\mathbf{k} = dl dm / \sqrt{1 - m^2 - l^2}, \\
 (\mathbf{k} \cdot \nu_1) &= m \sin \beta + l \cos \beta.
 \end{aligned}$$

The integration with respect to l is carried out from 0 to $\sqrt{1-m^2}$ as the angle, $\cos^{-1} l$, must lie between 0 and $\pi/2$ for a collision to be possible, while m is integrated from -1 to 1 . The integration covers two of the four quadrants so that because of symmetry the result must be doubled. For the integration with respect to the velocity elements, a linear transformation of the velocity components may be used (Loeb, 1934, p. 551).

The first integral of (11) vanishes as would be expected, since it does not depend upon the gradient, and is essentially the resultant force on a particle in a uniform gas without mass motion. The value of the integral in the second term of (11) is

$$-2/3 \pi^{7/2} \alpha_1^6 \alpha_3^3 \sqrt{m_1 + m_3} / \sqrt{m_3}$$

so that the complete term becomes

$$\frac{8\pi^{\frac{1}{2}} m_1 \sqrt{m_3}}{3\sqrt{m_1 + m_3}} \chi_{31} N_1 \sigma_{31}^2 \alpha_1 \omega_1. \quad (13)$$

The integral in the third term of (11) becomes

$$\pi^4 \alpha_1^5 \sigma_3^3 (m_1 + m_3) / 3m_3$$

so that the complete term becomes

$$-\frac{4}{3} \pi kT (\chi_{31} + .5a_1 N_1 - .5b_1 N_1) \sigma_{31}^3 \frac{\partial N_1}{\partial v_1}. \quad (14)$$

The integral of the last term of (11) was not successfully evaluated. Hence two special cases were considered—one in which α_1 is negligible compared with α_3 , and one in which α_3 is negligible compared with α_1 . In the former case, the integral vanished. In the latter, in which the thermal motion is negligible, we obtain for the complete term

$$-\frac{\pi kT m_3}{m_1 + m_3} \chi_{31} L_{12} \sigma_{31}^2 \frac{\partial N_1}{\partial v_1}. \quad (15)$$

Thus the desired expression must reduce to (15) for large m_3 but must vanish for $m_3 = 0$ even when the factor $m_3/(m_1 + m_3)$ is removed. Hence the expression will generally contain m_1 and m_3 and may be written approximately in the form

$$-\frac{\pi kT m_3^s}{(m_1 + m_3)^s} \chi_{31} L_{12} \sigma_{31}^2 \frac{\partial N_1}{\partial v_1}, \quad (16)$$

where $s > 1$.

The net force F_{31} , in the direction v_1 , is then given by the sum of the terms (13), (14) and (16), or introducing the expressions for ω_1 and L_{12} we have

$$\begin{aligned}
 F_{31} = & \frac{160}{27\pi} \sqrt{\frac{m_1 m_3 (m_1 + m_2)}{m_1 + m_3}} \frac{kT \chi_{31} N_1 \sigma_{31}^2}{N_1 + N_2} \\
 & \times \left[\frac{1}{\sqrt{2\sigma_1^2} N_1 \chi_{11} \sqrt{m_1 (m_1 + m_2)} + 2\sigma_{12}^2 N_2 \chi_{12} \sqrt{m_1 m_2}} \right. \\
 & \left. - \frac{1}{\sqrt{2\sigma_2^2} N_2 \chi_{22} \sqrt{m_2 (m_1 + m_2)} + 2\sigma_{12}^2 N_1 \chi_{21} \sqrt{m_1 m_2}} \right] \frac{\partial N_1}{\partial v_1} \\
 & - \frac{4}{3} \pi kT (\chi_{31} + .5a_1 N_1 - .5b_1 N_1) \sigma_{31}^3 \frac{\partial N_1}{\partial v_1} \\
 & - \frac{5kT m_3^3 \sqrt{m_1 + m_2} \chi_{31} \sigma_{31}^2}{3(m_1 + m_3)^3 \sqrt{2\sigma_1^2} N_1 \chi_{11} \sqrt{m_1 + m_2} + 2\sigma_{12}^2 N_2 \chi_{12} \sqrt{m_2}} \frac{\partial N_1}{\partial v_1}
 \end{aligned} \tag{17}$$

In the present development we are considering the mass velocity as due to diffusion only. In general, there may be a mass motion which does not vanish with diffusion. If this component is included, and the gradients vanish, then the resulting expression gives the force on a particle moving relative to the solvent. If $m_3 \gg m_1$ and $\sigma_3 \gg \sigma_{12}$ and $\chi_{31} = 1$, this reduces to the expression obtained by P. S. Epstein (1924, p. 720) and M. Smoluchowski (1906) for the force on a smooth particle which is small compared with the mean free path.

The force on the particle due to molecules of class 2 in the direction of the gradient of N_2 is given by an expression similar to (17) in which subscripts 1 and 2 are interchanged. The net force due to both types of molecules in the direction of the gradient of N_2 is given by $F_{32} - F_{31}$. We shall be especially interested in the case in which N_1 (solvent) is considerably larger than N_2 (solute) and in which m_3 is considerably larger than m_2 or m_1 , where generally $m_2 > m_1$. Now $\chi_{12} = \chi_{21}$ (Chapman and Cowling, 1939, p. 292) and χ_{11} because of the above restrictions is approximately equal to χ_{12} . The coefficient a_1 gives the amount by which a single class 1 molecule increases collision frequency between a class 1 molecule and the particle. This is of the order of the volume of the molecule, or because the molecular density is of the order of unity, we shall set $a_1 = m_1$, and similarly $a_2 = m_2$. The effect of a class 2 molecule on collisions between class 1 molecules and the particle is in general a more complex function, but again the effect per molecule, b_1 , is of the order of m_2 , at least if the particle is not too much larger than the molecules. We shall thus set $b_1 = m_2$.

and similarly $b_2 = m_1$. Then $\chi_{31} = \chi_{32}$. Under these assumptions we have for the net force $F_3 = F_{32} - F_{31}$,

$$F_3 = -\frac{kT \chi_{31} \sigma_3^2}{24 \chi_{11} N_1 \sigma_1^2} \left[(\sqrt{m_2} - 1.12 \sqrt{m_1}) \frac{\sigma_1^2}{\sigma_{12}^2} \sqrt{\frac{m_1 + m_2}{m_1 m_2}} + .16 \right] \frac{\partial N_2}{\partial \nu_2} - \frac{kT \sigma_3^2}{3} \left[\frac{3}{2} \chi_{31} (\sigma_2 - \sigma_1) + (m_2 - m_1) \sigma_3 N_1 \right] \frac{\partial N_2}{\partial \nu_2}. \quad (18)$$

If, in particular, the molecular diameters of molecules 1 and 2 are proportional to the masses, one can show that for $m_2 > m_1$, and $\sigma_2 > \sigma_1$, F_3 is negative, while for $m_1 > m_2$, $\sigma_1 > \sigma_2$, F_3 is positive. In general, this may not be so. However, from the above equation, one would expect a net outward force on particles in a volume element for which the divergence of the gradient of solute concentration, $m_2 N_2$, is negative (the solute being produced in the element) provided the solute molecules are larger than the solvent molecules; but one would expect an inward force on particles in the element if the solute is being produced, if they are smaller than the solvent molecules. This result is of interest in the diffusion force theory of cell division (Rashevsky, 1940).

The importance of the molecular properties of the molecules in determining the force is brought out in (18). It is also clear that the effect of the size of the molecules and particle becomes important as the density rises, especially since we wish the effect of the difference of two net forces. It might be pointed out that the viscosity of carbon dioxide was predicted for a range of values including some in the liquid state, suggesting that in liquids the momentum transport mechanism is similar to that in gases (Chapman and Cowling, 1939, p. 209). For a complex liquid like water, such a generalization is more doubtful.

We have considered the molecules as if they were smooth elastic spheres. If one considered various types of forces of interaction, different results would be obtained. In general, the result in such cases is very similar to the simplified case. If only numerical factors of the order of unity were involved, we would neglect them. But, since we are dealing with differences, and the factors might not be the same in the two opposing forces, it would be well to investigate under what conditions the results would materially differ from the present case.

Thus far we have had to restrict the diameter of the particle to values less than the mean free paths L_{12} and L_{21} . If the particle is much larger than the mean free paths, we may treat the solvent and solute as fluids flowing through each other. G. Young (1940) points out that in such a case the force due to the moving fluids is the sum

of the forces exerted by each fluid acting independently. If v_1 and v_2 are the velocities of solvent and solute due to interdiffusion, the particle being at rest, the force on the particle due to the solvent and solute are given by Stoke's law

$$\mathbf{F}_{31} = 3 \pi \eta_1 \sigma_3 \mathbf{v}_1, \quad (19)$$

$$\mathbf{F}_{32} = 3 \pi \eta_2 \sigma_3 \mathbf{v}_2. \quad (20)$$

The viscosity η_2 is taken to be that which the solute would have if it were a gas at the same temperature and density. The viscosity η_1 has a similar meaning, but as we shall consider the case in which $N_1 \gg N_2$, we may also refer to η_1 as the solvent viscosity.

The rate of mass transport, $d(m_1 N_1)/dt$, across a unit area is proportional to the gradient of the mass density and in the opposite direction. The proportionality constant is the diffusion coefficient D_{12} of the mixture. But this flow is just the velocity times the mass density. Thus

$$N_1 \mathbf{v}_1 = -D_{12} \frac{\partial N_1}{\partial v_1} v_1, \quad (21)$$

and a similar expression for the solute. The net force $\mathbf{F}_3$ is then, assuming $N_1 + N_2$ is a constant,

$$\mathbf{F}_3 = 3 \pi \sigma_3 D_{12} \left[\frac{\eta_2}{N_2} - \frac{\eta_1}{N_1} \right] v_2. \quad (22)$$

The expression for the diffusion coefficient as given by Einstein holds roughly for molecules, thus we may write approximately

$$D_{12} = \frac{kT}{3\pi \eta_1 \sigma_2}. \quad (23)$$

The expression for viscosity of a gas is

$$\eta = \frac{2 \psi \sqrt{kTm}}{3 \pi^{3/2} \sigma^2}, \quad (24)$$

where ψ is a factor introduced for dense gases, arising for the same reasons as χ . The viscosity of a dense gas is only slightly different from a rarified gas until the pressure is raised to many atmospheres. In the case of carbon dioxide, in which Enskog predicted the viscosity into the liquid state (Chapman and Cowling, 1939, p. 289), the range of variation is only about five. In the case of water, the range is much greater, being of the order of one hundred, indicating that other factors may enter, even considering the aggregation of molecules. For the sake of analogy, we may write the solvent viscosity in this form.

Making use of expressions (23) and (24), we obtain an expression for the force in the direction of the gradient of N_2 :

$$F_3 = \frac{kT \sigma_1^2 \sigma_3}{\sigma_2 \sqrt{m_1}} \left[\frac{\psi_2 \sqrt{m_2}}{\psi_1 N_2 \sigma_2^2} - \frac{\sqrt{m_1}}{N_1 \sigma_1^2} \right] \frac{\partial N_2}{\partial v_2}. \quad (25)$$

We are interested in the special case in which $N_1 \gg N_2$. If then N_1/ψ_1 is sufficiently greater than N_2/ψ_2 , we have approximately

$$F_3 = - \frac{\psi_2 kT \sigma_1^2 \sqrt{m_2} \sigma_3}{\psi_1 \sigma_2^3 \sqrt{m_1} N_2} \frac{\partial N_2}{\partial v_2}. \quad (26)$$

On the other hand for large enough N_2 , the sign of the force is reversed, and the expression for the force is approximately

$$F_3 = \frac{kT \sigma_3}{\sigma_2 N_1} \frac{\partial N_2}{\partial v_2}. \quad (27)$$

As we wish to consider the case in which $N_1 \gg N_2$, the solute would not be a particularly dense gas, so that continuing to neglect the effect of interaction, $\psi_2 = 1$. If the molecular densities are approximately the same for solvent and solute, equation (26) becomes

$$F_3 = - \frac{kT m_1^{1/6}}{\sqrt{m_2} \psi_1} \frac{\sigma_3}{N_2} \frac{\partial N_2}{\partial v_2}. \quad (28)$$

Comparing equations (26) and (18) one notes that in (26) the force varies only as the linear dimensions of the particle and depends on the gradient of the logarithm of the concentration, whereas in (18) the force varies with the square of the particle diameter, and with the gradient of the concentration. Also the force as given by (26) does not change sign when $m_2 < m_1$, $\sigma_2 < \sigma_1$. But from (25), if $m_2 \ll m_1$, and $\sigma_2 \ll \sigma_1$ and N_2 is not too much larger than N_1 , the sign of the force may change.

There are several reasons for the difference in form of the equations (18) and (26). In the kinetic theory treatment we consider that σ_3 is smaller than the mean free path, while in the second treatment, the assumption is made that σ_3 is considerably greater than the mean free path so that the fluid may be considered as continuous. This is just the reason for the difference in exponent of σ_3 as is discussed by P. S. Epstein (1924). The other basic type of difference is that of the appearance of the gradient of the logarithm of N_2 in (25). But it should be noted in the more general expression, from which (18) arises, N_2 does appear in the denominator. Furthermore, if instead of

the expression (9) for L_{12} , we use that value obtained by ignoring collisions of like molecules (cf. Stefan and Maxwell mass velocity, Loeb, 1934, p. 266), a term involving the gradient of the logarithm arises. As has been mentioned previously, the term in (18) containing the cube of the diameter is doubtful. On the other hand, in the derivation of (26) it was assumed that the viscosity, η_2 , of the solute has the value it would have if it were a gas at the same temperature and density.

In N. Rashevsky's derivation of the diffusion drag force on a particle of volume V_p , he obtained an expression,

$$F = - \frac{3RT}{2M} \alpha V_p \text{grad } c,$$

by considering a continuous pressure function due to molecular bombardments of a solute of molecular weight, M , and integrating over the surface of the particle to obtain the net force (cf. Rashevsky, 1938, chap. vii). The force on a molecule of the solvent was considered in a similar manner. He calculated the non-homogeneity of the solvent produced by this force, and showed that this nonuniformity results in a force on the particle in the opposite direction to the force due to the solute. Thus the above expression was obtained for the total force on the particle. However, in considering the solvent molecules as particles of sufficient size to consider a continuous pressure function, the opposing force due to the solvent was underestimated and the above α , instead of being about 0.7, becomes practically zero. Since some work has been done on the basis of that expression, it would be well to compare the order of magnitude of the net volume force on many particles which comprise a certain fraction, μ , of the solution, for biologically plausible values. In both cases, the net volume force is proportional to the gradient. The coefficient of the grad c from Rashevsky's equation is of the order of 10^7 for $\mu = .1$, $V_p \propto \sigma_3^3 \propto 10^{-18}$, $M \propto 10^2$. Using corresponding values in the corresponding expression from (18), together with values which follow from identifying the solvent with water, one finds the same order of magnitude for the coefficient of the grad c , $c = m_2 N_2$. The second term in (18) is found to be largest for these values. But this term is that remaining from the original terms due to the finite size of the particle, and is uncertain, since the treatment of the size of the particle and molecules was not at all complete. If this term was neglected, the resulting coefficient of grad c would be of the order of 10^2 to 10^4 instead of 10^7 , depending on the value of σ_3 as it varies in the range from 10^{-5} to 10^{-7} centimeters, thus materially reducing the magnitude of the force.

In the theory of forces in cell division, we are particularly interested in forces on particles in the range 10^{-7} to 10^{-5} cm. We shall estimate the order of magnitude of the force per cubic centimeter containing a number of particles which take up a fraction, μ , of the unit volume. Taking the fairly plausible values: $m_1 = 6 \times 10^{-23}$ gm., $m_2 = 2 \times 10^{-22}$ gm., $\mu = .1$, $N_1 = 10^{22}$, $N_2 = 10^{19}$, $(\partial N_2 / \partial r_2) = 10^{21}$, we have for the volume force from equation (26) on particles of sizes 10^{-7} , 10^{-6} , and 10^{-5} cm. the respective values 10^8 , 10^6 and 10^4 dynes cm^{-3} . Similarly from equation (18) we obtain the corresponding forces per unit volume: 6×10^7 , 3×10^7 , and 3×10^7 dynes cm^{-3} . The contributions from the first term of (18) are 10^6 , 10^5 and 10^4 respectively while those due to the second term of (18) are each 3×10^7 dynes cm^{-3} . In view of the previous discussion, the latter term is uncertain. In any case, the order of magnitude of the force per unit volume turns out to be of the order of magnitude of 10^4 to 10^7 dynes cm^{-3} . Using the above values for μ , M and for the gradient in the expression derived by N. Rashevsky (1940, chap. iii), one obtains for the force per unit volume a value about 10^7 dynes cm^{-3} , which is of the same order of magnitude or greater than that obtained above. Some of these estimates of the volume force are considerably lower than previously given, but we shall see in a paper to be published subsequently that a lower estimate is still adequate. It will be noted that the discrepancy between the first and second terms of (18) is smaller when forces per unit volume are considered than when the coefficients of the concentration gradient are compared.

Summary. An expression has been derived for the force on a particle in a non-uniform mixture of gases. The size of the molecules and particle has been taken into account only in an approximate manner. An attempt is made to extrapolate the results to liquids, and using biologically plausible values for the various parameters, the force on particles in a unit volume is estimated. A similar expression for the force on a particle is obtained on hydrodynamic grounds and the latter expression is compared with the former. A similar estimate of the force per unit volume is made. The two estimates are of about the same order of magnitude. These results are also compared with the expression obtained by N. Rashevsky. Although his treatment was not adequate, the order of magnitude of the force per unit volume comes out about the same. Thus subsequent work based on his equation, especially in the problem of cell division are probably not basically affected.

The author is indebted to Dr. N. Rashevsky for suggesting the problem and to Dr. A. S. Householder for checking the calculations.

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A MATHEMATICAL ANALYSIS OF ELONGATION AND CONSTRICTION IN CELL DIVISION

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An equation for the rate of elongation of a dividing egg is integrated and generalized. The rates of elongation and constriction of a number of eggs under various conditions are analyzed and compared with the theoretical predictions. The theory accounts rather well for a large body of data on elongation and constriction. The general shapes of the elongation and constriction curves are predicted and the orders of magnitude of the parameters are satisfactory. One of the parameters for the elongation curves is related theoretically to the parameter of the constriction curves, and the correct order of magnitude is obtained if one parameter is predicted from the other.

The factors involved in cytokinesis are many and varied and the influence of various chemicals and physical changes on the process have been studied extensively. Several theories have been advanced as to the source of the mechanical forces involved in the process of deforming the cell (cf. Wilson, 1925). Included in these hypotheses are such factors as changes in form of the astral figure (Chambers, 1924; Gray, 1931), production of a coagulating principle (Burrows, 1927), variation in surface forces over the cell surface (Spek, 1918), forces of an electrical nature, changes in permeability (Lillie, 1918), changes in viscosity due to sol-gel transformations (Chambers, 1938; Marsland, 1939), equatorial intrusion and polar pseudopodial movements (Schechtman, 1937), osmotic forces and drag forces due to diffusion of metabolites (Rashevsky, 1938).

It is possible to divide oil drops by reducing the oil—water tension on two sides with a resulting elongation in the direction of minimum tension (Spek, 1918; Wilson, 1925). The possible effect of surface forces varying axially has been considered theoretically by G. Young (1939a) for the case of a true surface tension with a variation of the tension along the surface. Depending on how the tangential stress is sustained, one can obtain either shortening or elongation for a given case. The effect of surface forces will be discussed in greater detail subsequently. Calculations by N. Rashevsky (1938) and R. Williamson (1939) indicate that the effect of electrical forces would be small compared to those of diffusion. In the above mentioned hy-

potheses, except the last, little attempt has been made to predict any quantitative changes or to develop any mathematical theory of the effect of the various factors. Just how the forces arise is not clear in most cases. This in no way invalidates them, but makes difficult a mathematical treatment of the theories, at least until some investigation is made concerning the manner in which the forces arise. However, a considerable number of facts can be brought together with their aid. Theoretical investigation along these lines is definitely suggested. In the present paper we shall limit our discussion to the case in which only diffusion forces, osmotic forces and surface tension act, and in which viscosity opposes motion.

The nature of diffusion drag forces has been discussed in a number of papers (Rashevsky, 1938; Young, 1938; Landahl, 1942). As part of a program to investigate theoretically possible factors involved in cell division, this type of force has been considered (Rashevsky, 1938; Young, 1939), and certain predictions regarding elongation and constriction have been obtained. It is our purpose to extend some of these results, compare the predictions with experimental data, and to discuss the implications of the restrictions thus imposed on the parameters.

A COMPARISON OF THE ELONGATION EQUATION WITH EXPERIMENTAL DATA

An equation for the elongation of freely dividing cells as a function of time. We start with the expression for the rate of elongation given by N. Rashevsky (1940, chap. iii, eq. 44):

$$\frac{r_1}{r_1 - r_2} \frac{dr_1}{dt} = \frac{K}{1 + \frac{1}{2}(1+b)\frac{r_0^3}{r_1^3} + b\frac{r_0^{3/2}}{r_1^{3/2}}} - \frac{\gamma r_1^{3/2}}{2\eta r_0^{3/2}}, \quad (1)$$

where

$$K = \frac{RTq\mu r_0^3}{4M\eta D_e} \quad (2)$$

and

$$b = \frac{2D_i}{D_e}. \quad (3)$$

The parameters $2r_1$ and $2r_2$ are the length and width of a cell whose diameter is $2r_0$ in the spherical shape; γ is the surface tension, η the viscosity of the interior of the cell, t the time, D_e and D_i the effective external and internal diffusion coefficients, q the effective rate of production of metabolites of average molecular weight M , μ the

fractional volume of non-solvent particles on which the diffusion forces act, T the temperature and R the gas constant (Rashevsky, 1940). In view of subsequent work (Landahl, 1942), the expression for K is actually more complex than given by (2), but about of the same order of magnitude.

Equation (1) is not expected to hold for too great elongations. Thus let

$$\varepsilon = (r_1 - r_0)/r_0. \quad (4)$$

The volume is practically constant, and is given by

$$V = \frac{4}{3} \pi r_1 r_2^2 = \frac{4}{3} \pi r_0^3. \quad (5)$$

From (4) and (5) we have r_1 and r_2 in terms of ε . Introducing these values into (1), expanding and retaining only the first three terms of the expansions, and rearranging, we obtain

$$\frac{d\varepsilon}{dt} = A\varepsilon - B\varepsilon^2 - C\varepsilon^3, \quad (6)$$

where

$$A = \frac{1}{r_0} \left[\frac{K}{(1+b)} - \frac{3\gamma}{4\eta} \right], \quad (7)$$

$$B = \frac{1}{4r_0} \left[\frac{K}{(1+b)^2} (1-3b) + \frac{3}{4} \frac{\gamma}{\eta} \right], \quad (8)$$

$$C = \frac{1}{24r_0} \left[\frac{K}{(1+b)^3} (19+50b+7b^2) - \frac{3}{4} \frac{\gamma}{\eta} \right]. \quad (9)$$

Integrating (7) and solving for t , we obtain

$$t = t_0 + \frac{1}{2A} \log \frac{\varepsilon^2}{A - B\varepsilon - C\varepsilon^2} + \frac{B}{2A\sqrt{B^2 + 4AC}} \log \frac{\sqrt{B^2 + 4AC} + B + 2C\varepsilon}{\sqrt{B^2 + 4AC} - B - 2C\varepsilon} \quad (10)$$

Starting with a more complete equation (Rashevsky, 1940, chap. iii, eq. 14) including the permeability, h , so that osmotic forces are taken into account, we obtain as above an expression of the form (10). The parameters corresponding to A , B and C are now rather complex, and are of the form

$$A' = \frac{1}{r_0} \left[K' - \frac{3\gamma}{4\eta} \right], \quad (11)$$

$$B' = \frac{1}{4r_0} \left[G_1 K' + \frac{3\gamma}{4\eta} \right], \quad (12)$$

$$C' = \frac{1}{24r_0} \left[G_2 K' - \frac{3\gamma}{4\eta} \right], \quad (13)$$

where

$$K' = \frac{RTqr_0^3}{12M\eta} \frac{3\mu r_0 h - D_e(2 - 3\mu)}{2D_i D_e + r_0 h(2D_i + D_e)}, \quad (14)$$

and the factors G_1 and G_2 depend upon the value of b as defined above, as well as upon the extent to which $3r_0 h$ exceeds $D_e(2 - 3\mu)$. The actual expressions for G_1 and G_2 are very complex and so are not given here.

As μ would not exceed about one-third, and is probably not less than one-twentieth, the requirements that the $K' > 0$ is that $r_0 h$ be larger than D_e by a factor from $\frac{1}{2}$ to 10 depending on μ . If $r_0 h > D_e$, it follows from the expression for Λ , the total diffusion resistance of a spherical cell (Rashevsky, 1940, chap. i, eq. 21 and 23), that the contribution to the resistance due to the external medium is greater than that due to the plasma membrane. This is not so for relatively impermeable substances and in particular is not so for oxygen if one uses the known values of D_e , r_0 and the estimated value for h (Landahl, 1937; Rashevsky, 1940, chap. ii) for eggs with outer membranes. However, the permeability without the outer membrane may be considerably larger. If it is larger by a factor of about ten, then we would have $r_0 h > D_e$. For many metabolites not enough information is known and thus we cannot arrive at any conclusions. The restriction is an important one, and must be considered in greater detail eventually, but we shall not do so here. If $r_0 h < D_e$, but if $q < 0$, division is still possible for certain cell sizes. This case has been discussed by N. Rashevsky (1940, chap. iii).

The effect of the variation of production rate with concentration on the elongation equation. In the development of the elongation equation, it has been assumed that q was essentially a constant. We may inquire as to the effect of a q which depends upon the concentration. One might wish to consider the case in which the production, q , is proportional to the average concentration, or the case in which there is a constant production but a resynthesis going on proportional to the concentration. These cases can be summarized in the expression

$$q = q_0 + a\bar{c}. \quad (15)$$

For the first mentioned case $q_c = 0$, while for the second case $a < 0$.

Using the approximation method (Rashevsky, 1940), we may derive the expression for elongation. The expression is cumbersome, but if we proceed as above, we may obtain an expression for the rate as a parabola (see next section) in which instead of A we use the expression A' given by

$$A' = A \left[1 + \frac{ar_0^2(1+b)}{9D_i} \right] \quad (16)$$

and instead of B the expression B' given by

$$B' = B \left[1 + \frac{ar_0^2(1+b)}{9D_i} + \frac{ar_0^2A}{9D_eB} \right]. \quad (17)$$

A and B are again given by (7) and (8) but instead of q in K of equation (2) we write $q_0 + ac_0$, where c_0 is the external concentration. The third term in the brackets of (17) is less than the second, since $D_e > D_i$ and $B > A$. Thus, A' and B' differ from A and B by the factor in the brackets of (16). As $q = q_0 + ac_0$, $a < q/c_0$ for $a > 0$. For *Arbacia* eggs the factor may be written approximately as one plus a quantity of the order of, or less than, $q/(bc_0)$. Unless b and c_0 are taken to be smaller than would ordinarily be expected, this latter term is smaller than one, and A' and B' are approximately the same as A and B respectively. On the other hand, if the value of $q/(bc_0)$ is larger than one, A and B would be changed by about the same amount. If this term is considerably greater than one, the approximation method breaks down seriously. One could perhaps allow for a factor of the order of ten.

If a is negative, A' and B' may be reduced in magnitude. If the factor $q/(bc_0)$ is small, we may disregard it and we may drop the primes. If the factor approaches unity, then A' may be appreciably less than A , and B' might become negative. This is a rather special case. If the factor exceeds unity, A' is negative. But we are only interested in A' greater than zero, since this is the case for dividing eggs.

From the above results, we see that the difference between a constant rate of production, q , and a q proportional to concentration or a q which increases or decreases linearly with concentration, is slight as far as its effect on the slope of the elongation curve is concerned. The parameters may be changed by a fairly large factor, but the ratio of A to B will probably not be affected appreciably.

The effect on the elongation curve of a force proportional to the gradient of the concentration compared with that due to the gradient of the logarithm of the concentration. In a previous paper (1942) it was seen that the force might be proportional to the gradient of the logarithm of the concentration $c = mN$, rather than to gradient c . The result is that, if the force is derived from a potential, the latter is proportional to $\log c$. It is the difference in potentials at the "ends" and "sides", $\log c_1 - \log c_2$, that enters into the elongation equation (Rashevsky, 1940, p. 43, for $h = \infty$). But this is $\log (c_1/c_2)$. Only small differences of concentration are required to produce a considerable effect. Thus, c_1 is of the order of c_2 and hence $\log (c_1/c_2)$, which is equal to $\log [1 + (c_1 - c_2)/c_2]$, is approximately $(c_1 - c_2)/c_2$. Since the difference $c_1 - c_2$ varies much more than c_2 , we may treat c_2 as a constant for a first approximation. We then have the same result that would be obtained if the force were proportional to gradient c . Thus whether the force is proportional to gradient c or to gradient $\log c$, the resulting expression for elongation is the same to a first approximation.

A general comparison of the equation of elongation with experimental data. Timed photographs of dividing *Arbacia* eggs during division were made by R. Buchsbaum and R. Williamson (1942) for the purpose of testing some of the theoretical conclusions which follow from the diffusion drag force hypothesis. Some measurements of elongation of *Arbacia* eggs are given by L. Churney (1936, 1940), but no constriction measurements were made simultaneously as would be necessary for our discussion. We shall confine our considerations to the data first mentioned. In most cases the eggs were denuded of the fertilization membranes. These cells without membranes elongate markedly during the process, taking on a dumb-bell shape. It is this process of elongation which we are considering. After elongation ceases, the egg slowly shortens to some extent. For the present this effect will not be considered.

The rate of change of the relative elongation with time is given by equation (6). The parameter A must be positive. A negative A would correspond to a case in which a cell became shortened before beginning to elongate. Since this is not observed, A must be positive. Then for $A > 0$, it follows that $C > 0$. The parameter B is positive if $b \leq 1/3$, and negative if $b \geq 1$. It changes sign at some point in this interval depending on the values of A and K . If $B = 0$ and $C > B$, we may ignore the last term and the expression is a parabola. On the other hand if B should be very much smaller than C we may drop that term and we have the rate given by the linear and cubic

terms. If B and C must both be taken into account, one will generally have a curve whose shape is intermediate. If one normalizes the expression so that the maximum value of the rate, ε'_m , is unity, and the value of ε , ε_m , at which ε' returns to zero is also unity, then the shapes of the curves may be readily compared. Designating the normalized variables as ε'^* and ε^* , the expressions corresponding to $B = 0$ and $C = 0$ are respectively

$$\varepsilon'^* = \frac{3\sqrt{3}}{2} \varepsilon^* (1 - \varepsilon^{*2}), \quad (18)$$

$$\varepsilon'^* = 4\varepsilon^* (1 - \varepsilon^*). \quad (19)$$

These expressions have no arbitrary parameters and enable us therefore to compare data obtained on different cells. Thus, if the curves for these expressions are graphed, one should expect that any experimental data, to which they are to be compared, should lie between them if there were no error of measurement. In Figure 1, these

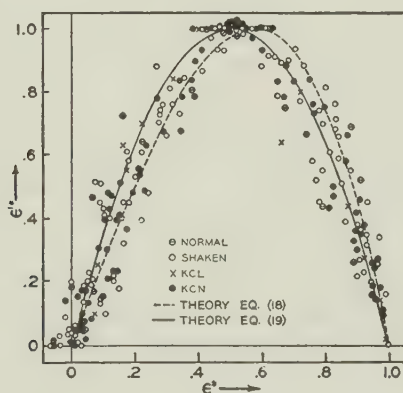


FIGURE 1

expressions are graphed, the former expression being shown as a broken line, the latter as a solid curve. To test this expectation, the measurements of the slopes of the elongation curves were made from each of thirty-four eggs under various conditions. These values were normalized in the sense used above and plotted in Figure 1. A discussion of the specific cases will be given later. The various symbols used to represent the measurements are explained in the figure. For each curve, the slopes were determined at about six to ten points. The scatter in the measurements is rather large as may be expected from measurements of slopes. However, within the range of error, it is clear that the average trend of the data lies approximately within the range of

the theoretical curves. The absence of arbitrary parameters in the theoretical curves increases the significance of the agreement. To the extent of the agreement we may say that the form of the experimental curve is predicted correctly by the theory.

It will be noted that the data scatter about the origin. The origin is determined in each case by the initial radius r_0 as determined by proper average of several measurements of cell diameters prior to appreciable elongation. Some cells appear slightly elongated for some time prior to beginning of elongation for division while others are slightly compressed. A few showed a slight shortening before beginning to elongate. This may be due in part to changing in position of the cells as discussed by L. Churney (1936). If this is the case, the variation caused should be randomly distributed, and one would still be justified in using the initial trend. This effect is only appreciable near the origin. It should also be pointed out that the approximations made in deriving the original expression (1) begin to break down at about the maximum of the curve. Without a more detailed investigation, one cannot expect agreement in the latter part of the curve, but it may be considered as an extrapolation.

The fact that a parabola is a fairly good approximation to the experimental curve as shown in Figure 1 suggests that one might use only the first two terms of (6). This could be done only if the values of the parameters are not significantly altered. If one first assumes C to be zero, and determines A and B from a comparison with the experimental curve, the parameters K and γ/η are obtained from equation (7) and (8). Similarly one can obtain these parameters by assuming $B = 0$. It is found that essentially the same values are found for K and γ/η in each case. The value of K obtained in the second case varies only by a factor 4 when b varies from 0 to 2, while γ/η varies less than about $1/2$, unless b becomes large enough to make B negative when this can occur. But then C must necessarily play the dominant role and we thus obtain essentially the same values for K and γ/η , unless B takes on so large a negative value that a much larger value is obtained for C from the complete expression than would be the case when B is set equal to zero. We shall thus for simplicity drop the $C\epsilon^3$ term as well as b in most of the further discussions. Instead of equation (10) we have

$$\epsilon = A/(B + Ae^{-A(t-t_0)}), \quad (20)$$

where t_0 is an integration constant. A and B are given by expressions (7) and (8) so that we have, solving for K and γ/η ,

$$K = r_0(A + 4B)/2, \quad (21)$$

$$\gamma/\eta = 2r_0(4B - A)/3. \quad (22)$$

Eggs with membranes. In the process of division, eggs with membranes elongate about twelve per cent (cf. Churney, 1936). The membrane appears to act only as a restraining sac which is elastic, and can be considered as outside the cell proper. One should then probably replace the surface tension γ by a more complex expression. We shall, however, evaluate the parameters on the basis of the same equation.

The curves of elongation of five eggs at first cleavage with fertilization membranes intact were plotted and the parameters A and B determined. One of these eggs had been treated in 10^{-4}M KCN for twenty minutes and had been shaken. A second egg had also been shaken. The relative error is large because the amount of elongation is small, but the ranges of values for A and B were not large. The parameters A and B as well as the time from fertilization to first division from the KCN treated egg did not take on values outside of the range of the other eggs. The average value of A for the other eggs was $0.025 \pm 5 \text{ sec.}^{-1}$ while the value of B was $0.22 \pm 3 \text{ sec.}^{-1}$. No values varied by more than fifty per cent of these averages. From these values, we find $K = 1.7 \times 10^{-3} \text{ cm. sec.}^{-1}$ and $\gamma/\eta = 2.1 \times 10^{-3} \text{ cm. sec.}^{-1}$. Further discussion of these values will be made subsequently. The average value of maximum elongation, ε_m , was $\varepsilon_m = .12 \pm 1$, while the average of the maximum slope, $(d\varepsilon/dt)_m = \varepsilon'_m$, was $\varepsilon'_m = 3.7 \pm 9 \times 10^{-4} \text{ sec.}^{-1}$. The average value of the time from fertilization to beginning of division t'_0 , as measured by the intercept of the line of maximum slope with the line $\varepsilon = 0$, was found to be $t'_0 = 48 \pm 3 \text{ min.}$ The value t'_0 is more easily determined than t_0 of equation (20), and is about two minutes less than the latter, the latter being approximately the time to the inflection point. The average initial diameter was $2r_0 = 74 \pm 2 \times 10^{-4} \text{ cm.}$ The number after the $\pm$ sign in each case gives the mean variation about the average. In this case it was estimated on the basis of values from the five eggs.

Eggs with membranes removed by shaking. Sixteen elongation curves of eggs with the fertilization membranes removed by shaking were selected as being suitable to compare with the theoretical equation (20). The parameters were thus found to have the values $A = 0.024 \pm 4 \text{ sec.}^{-1}$ and $B = 0.059 \pm 9 \text{ sec.}^{-1}$. From these values we obtain $K = 4.5 \times 10^{-4} \text{ cm. sec.}^{-1}$ and $\gamma/\eta = 4.9 \times 10^{-4} \text{ cm. sec.}^{-1}$. Other average values are: $\varepsilon_m = .40 \pm 5$, $\varepsilon'_m = 2.3 \pm 3 \times 10^{-3} \text{ sec.}^{-1}$, $t'_0 = 46 \pm 4 \text{ min.}$, $2r_0 = 69.5 \pm 15 \times 10^{-4} \text{ cm.}$ Comparing these values with those from eggs with membranes, we see that not only the extent of elongation is greater without membranes, but the maximum rate is

about six times as large. The values t'_0 and r_0 are essentially the same, as is also the parameter A . But B is much smaller, so that K and γ/η are both smaller, especially γ/η . A sample curve is shown in Figure 2a. The curve of constriction will be discussed later. In this

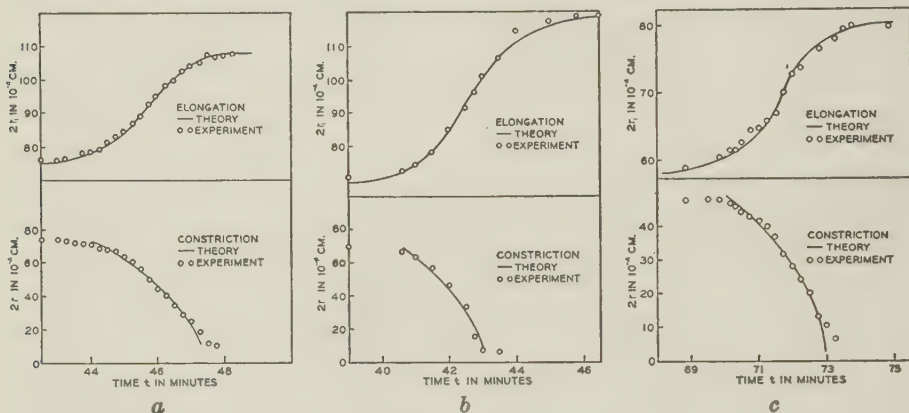


FIGURE 2

case there are more points than there are for most curves. The parameters are $A = .029 \text{ sec.}^{-1}$, $B = .069 \text{ sec.}^{-1}$, $t_0 = 46.1 \text{ min.}$, and $2r_0 = 75.5 \times 10^{-4} \text{ cm.}$ This value is obtained by extrapolating the slope curve to zero and is two per cent higher than that obtained by averaging several diameters.

Eggs with membranes removed by KCl treatment. Two elongation curves from eggs with membranes removed by treatment with KCl were used to obtain the various parameters. The eggs did not show any hyaline material on the surface. The values of the parameters are: $A = .019 \text{ sec.}^{-1}$, $B = .032 \text{ sec.}^{-1}$, $\epsilon_m = .58$, $\epsilon'_m = 2.7 \times 10^{-3} \text{ sec.}^{-1}$, $t'_0 = 44.7 \text{ min.}$, $2r_0 = 73.0 \times 10^{-4} \text{ cm.}$, and $A = .021 \text{ sec.}^{-1}$, $B = .029 \text{ sec.}^{-1}$, $\epsilon_m = .71$, $\epsilon'_m = 4 \times 10^{-3} \text{ sec.}^{-1}$, $t'_0 = 40.8 \text{ min.}$, $2r_0 = 69.2 \times 10^{-4} \text{ cm.}$, giving the average values $K = 2.6 \times 10^{-4} \text{ cm. sec.}^{-1}$ and $\gamma/\eta = 2.4 \times 10^{-4} \text{ cm. sec.}^{-1}$. The latter curve is shown in Figure 2b, where $t_0 = 42.9 \text{ min.}$ Comparing with the values from eggs with membranes removed by shaking, we find that the extent of elongation is significantly increased, that the maximum rate probably increased, that A remained essentially unchanged, and B decreased about one-half, so that K and γ/η decreased, especially the latter.

Eggs with membranes removed by shaking and treated with KCN. Twelve elongation curves from eggs without membranes and treated with KCN were used to determine various parameters. There is some variation in both the concentration of KCN and time of treatment, but we shall treat the group as a whole. In most cases, the

concentration was between 10^{-4} and 10^{-5} M and the eggs remained in the solution from a short time after insemination. The average values of the various parameters obtained are: $A = .020 \pm 3 \text{ sec.}^{-1}$, $B = .048 \pm 9 \text{ sec.}^{-1}$, $\varepsilon_m = .44 \pm 2$, $\varepsilon'_m = 2.2 \pm 4 \times 10^{-3} \text{ sec.}^{-1}$, $t'_0 = 57 \pm 7 \text{ min.}$, $2r_0 = 68.4 \pm 7 \times 10^{-4} \text{ cm.}$, $K = 3.6 \times 10^{-4} \text{ cm. sec.}^{-1}$, and $\gamma/\eta = 3.9 \times 10^{-4} \text{ cm. sec.}^{-1}$. Comparing these values with those from eggs treated the same but without KCN we find that the effect of the KCN is noticeable in the increase in t'_0 . The other differences are not at all significant.

Eggs with membranes removed by shaking, second cleavage. Three cells with membranes removed by shaking were followed into second cleavage. From six curves, the following values were found: $A = .025 \pm 3 \text{ sec.}^{-1}$, $B = .071 \pm 12 \text{ sec.}^{-1}$, $\varepsilon_m = .35 \pm 2$, $\varepsilon'_m = 2.3 \pm 3 \times 10^{-3} \text{ sec.}^{-1}$, $t'_0 = 72 \pm 2 \text{ min.}$ from insemination, $2r_0 = 58 \pm 1 \times 10^{-4} \text{ cm.}$, $K = 4.5 \times 10^{-4} \text{ cm. sec.}^{-1}$, and $\gamma/\eta = 5 \times 10^{-4} \text{ cm. sec.}^{-1}$. The values of $2r_0$ could not be measured with much accuracy, because the cells were not sufficiently regular. The values used here were determined by extrapolating the curves, and are perhaps ten per cent too high. Comparing the values of the parameters of second cleavage with those of first cleavage, we find the values are almost identical, or not significantly different except for t'_0 and $2r_0$ which are necessarily different. The value for $2r_0$ for the half cells should be 0.8 that of the whole cell. A sample curve is shown in Figure 2c, where $A = .025 \text{ sec.}^{-1}$, $B = .065 \text{ sec.}^{-1}$, $t_0 = 72.2 \text{ min.}$, and $2r_0 = 58 \times 10^{-4} \text{ cm.}$

Discussion. In the early stages of the development of a theory, one does not expect too much agreement with experiment. When predictions can be made, they should be tested. If the prediction is verified by experiment, further development of the theory is suggested. If the prediction is not borne out, it is necessary to interpret the meaning of the failure on the basis of the theory, modify the theory, or suggest how other factors, which have not been considered may be responsible. It is essential that the order of magnitude of the parameters be in agreement with values obtained by substituting plausible values of the more basic constants of which they are made up. The expression of K is given in equation (1). As discussed previously (Landahl, 1942), the expression for K is more complex, but the order of magnitude is probably not much changed. If we take $\mu \sim 10^{-1}$, $M \sim 10^2$, $D_e \sim 5 \times 10^{-6}$, and $\eta \sim 10^{-1}$, then since $K \sim 5 \times 10^{-4}$, we find that it is sufficient that q be of the order of $10^{-9} \text{ gm. cm.}^{-3} \text{ sec.}^{-1}$. The parameter q is to be considered an effective rate of production, and thus may be of the order of, or less than the q values of the most rapid processes, those of respiration. This value is well below those

for respiration (Rashevsky, 1940, chap. ii). The value of K is thus found to be satisfactory. A possible increase in A and B , discussed in the preceding section, would thus be taken into account.

However, equation (2) predicts that, other things being constant, K should be proportional to the volume of the cell. It would seem, that for a half cell, the value of K should then be half that of the whole cell. This is not borne out here, but is for the case of constriction to be discussed subsequently.

The value of γ/η would be of the order of unity if we take $\gamma \propto 10^{-1}$ and $\eta \propto 10^{-1}$ as above. Comparing this with the values obtained, we find a factor of several thousand. It might be pointed out in this connection that this is just the factor obtained by E. N. Harvey and H. Shapiro (1941) between the "relaxation" times of cells deformed by squeezing and cells deformed by centrifuging. The value of γ for fertilized eggs without membranes could probably be considerably smaller than that estimated from unfertilized eggs. The value of the viscosity of dividing eggs is considerably higher than that of unfertilized eggs. Another possible explanation lies in the simplification of the expression for γ/η by assuming that $b = 0$, or that $2D_i < D_e$. It is readily shown that the effect of increasing b is to increase both K and γ/η roughly by the factor $1/(1 - b)$. But this alone is hardly sufficient. Another factor was mentioned in a preceding sub-section which allows an increase of perhaps ten. These factors taken together could account for the discrepancy.

An important factor not considered is that some of the parameters, especially q , probably vary with time due to the numerous changes which are taking place. The introduction of such an effect should also make it possible to predict the elongation curve beyond the point of maximum into the region in which shortening again takes place. It has been suggested by R. Williamson that a factor which should be taken into account in this connection is the disturbance of the diffusion fields of each cell by its neighbor. This could result in equilibrium shapes other than a sphere.

One might expect that γ/η would be larger for cells with membranes. This is found to be the case, the increase being by a factor of 4.3. However, K also was found to be larger, though not by quite as large a factor. This might be interpreted as implying that D_e is decreased, thus K increased, by the presence of the membrane, as the latter is essentially external to the cell.

Summary. We have seen that the shape of the experimental elongation curve is predicted fairly well by the theory, as illustrated by Figures 1 and 2. In the composite plot of values, as shown in Fig-

ure 1, the trend may deviate somewhat at the very beginning, producing a slight inflection. Aside from this, the entire positive part of the experimental curve of elongation rate with time is a parabola. The parameters of the elongation curves are given for various experimental conditions. The value of the parameter γ/η appears to be too small compared with the ratio of γ to η , estimated directly. Factors are discussed which can account for this apparent discrepancy. The parameter K is of an order of magnitude consistent with the expressions given by equation (2).

A COMPARISON OF THE CONSTRICTION EQUATION WITH EXPERIMENTAL DATA

An expression for the constriction rate for advanced stages was derived by G. Young (1939b). A more detailed treatment, though only approximate, was given by N. Rashevsky (1941) which indicated that the results first mentioned might hold for a large part of the constriction process. The expression is given by (Rashevsky, 1940, chap. iii)

$$r^2 = r'^2 - 2Qt, \quad (23)$$

where $2r$ is the width of the "neck", r' is an integration constant and

$$Q = Kr_0/88, \quad (24)$$

in which K is given by equation (2).

The extent to which the equation agrees with the data is illustrated in Figures 2a, 2b, and 2c. In some cases the curve remained essentially straight or showed an inflection in about the middle part of the curve. Where a curve was concave downward to beyond half constriction, that part of the curve was used if possible. A small number of curves could not be used, most of which were from the same batch of eggs. A few others were not used because the points were too scattered or too few.

For each of the curves used, the point of inflection was estimated. Three-fourths of the curves showed inflection points below $r = 26 \times 10^{-4}$ cm. One-half of the curved showed inflection points below $r = 20 \times 10^{-4}$ cm., and one-fourth below 13×10^{-4} cm. As one measured values of $2r$ below the inflection point it became increasingly uncertain as to whether the furrow width was being measured, especially in eggs in which the daughter cells tended to adhere.

The curves are not given beyond r_0 since the equation necessarily breaks down at some value $r < r_0$. For small widths, less than about 6×10^{-4} cm., measurements could not be made with accuracy from the

photographs. Furthermore, at about this stage one would expect secondary necking to begin. But the situation is complicated by the presence of strands from the spindle fibers connecting the daughter cells.

Eggs with membranes. Six eggs with membranes, two having been treated with KCN, were measured and the parameters r' and Q were obtained. The two KCN showed no significant difference from the others and were thus included to estimate the mean error. The average values obtained were: $r' = 1.3 \pm 1 \times 10^{-2}$ cm., $Q = 2.6 \pm 3 \times 10^{-8}$ cm.² sec.⁻¹, so that from equation (24), $K = 6.2 \pm 7 \times 10^{-4}$ cm. sec.⁻¹. This value of K is somewhat less than one-half of the value obtained from the corresponding elongation curves.

Eggs with membranes removed by shaking. The same group of eggs with membranes removed by shaking were measured for the determination of r' and Q , giving the following average values: $r' = 1.3 \pm 1 \times 10^{-2}$ cm., $Q = 2.9 \pm 3 \times 10^{-8}$ cm.² sec.⁻¹, from which $K = 7.3 \pm 8 \times 10^{-4}$ cm. sec.⁻¹. The value obtained for this group of eggs from the elongation curves is about forty per cent smaller than this value of K . The values of Q , r' and K are not significantly different in the eggs with and without membranes. An illustration of the constriction curve from an egg of this group is shown in Figure 2a where the parameters are $r' = 1.38 \times 10^{-2}$ cm. and $Q = 3.36 \times 10^{-8}$ cm.² sec.⁻¹.

Eggs with membranes removed by KCl treatment. The two eggs with membranes removed by KCl gave the following values of the parameters: $r' = 1.4 \times 10^{-2}$ cm., $Q = 3.7 \times 10^{-8}$ cm.² sec.⁻¹, $K = 8.9 \times 10^{-4}$ cm. sec.⁻¹, and $r' = 1.5 \times 10^{-2}$ cm., $Q = 4.2 \times 10^{-8}$ cm.² sec.⁻¹, $K = 10.6 \times 10^{-4}$ cm. sec.⁻¹. Both these values of Q , and also K , are above almost all of the other values while the value of K from the elongation curves decreased. The significance of Q will be discussed subsequently. An illustrative curve from the second of these eggs is shown in Figure 2b.

Eggs with membranes removed by shaking and treated with KCN. From these eggs the average values of the parameters are: $r' = 1.4 \pm 1 \times 10^{-2}$ cm., $Q = 2.8 \pm 3 \times 10^{-8}$ cm.² sec.⁻¹, $K = 7.2 \pm 8 \times 10^{-4}$ cm. sec.⁻¹. Comparing these values with those obtained from the eggs similarly treated but without KCN we find them to be the same, that is, the curves are essentially unchanged by the KCN treatment, although the time to division was increased by about twenty-five per cent. There was no significant change in K from the elongation curves due to KCN treatment.

Eggs with membranes removed by shaking, second cleavage. From the measurements of the constriction of the second cleavage eggs, the following parameters were obtained: $r' = 1.2 \pm 1 \times 10^{-2}$ cm., $Q = 1.5 \pm 2 \times 10^{-8}$ cm.² sec.⁻¹, $K = 4.8 \pm 6 \times 10^{-4}$ cm. sec.⁻¹. Compar-

ing these values with those from the first cleavage we see that Q and K are significantly smaller here. The value of K from elongation did not show this change. From these comparisons we find that the constriction rates are very much the same except for the half eggs. This suggests that the size of the cell may play a role. But this is already predicted by the definition of Q and K . In Figure 2c is a sample curve from this group for which the parameters are $r' = 1.24 \times 10^{-2}$ cm., and $Q = 1.75 \times 10^{-8}$ cm.² sec.⁻¹.

The relationship between Q and r_0 . From equations (24) and (2) we expect that Q should vary with r_0^4 . But from recent studies (Landahl, 1942), we would expect K to be proportional to r_0^2 instead of to r_0^3 . Thus Q should be proportional to r_0^3 . For this reason the values of Q from each of forty-six eggs were plotted with the initial radius r_0 . The resulting graph is shown in Figure 3. The same sym-

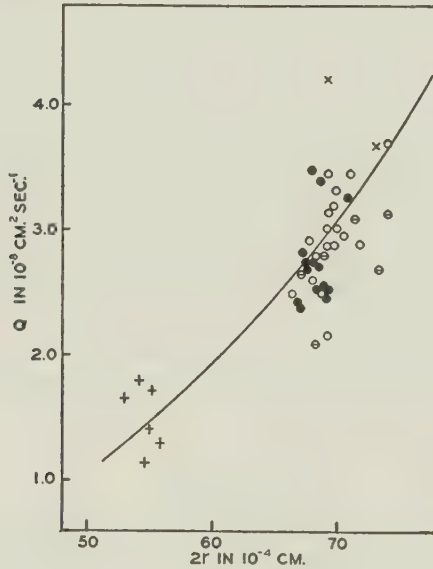


FIGURE 3

bols are used here as before, but in addition the values from half cells are designated by a plus sign. From the figure, one might suspect that the KCl eggs are different. In any case the correlation between Q and r_0 , not including the half eggs or the KCl treated eggs is found to be 0.6 ± 1 . This correlation is decreased by including the eggs treated with KCl. The curve of Figure 3, which has but one parameter, is given by $Q = 0.72r_0^3$. Thus, this prediction is at least in part borne out. If one uses the fourth power relation given by (2) and (24), $Q = 220r_0^4$, the agreement is poorer. The value of Q from sec-

ond cleavage was close to one-half that at first cleavage. The values of $2r_0$ for the half cells were difficult to estimate. They were about five per cent less than that which would be obtained by assuming that each daughter cell contained one-half the original volume. In the case of eggs treated with KCl, the measurements could be made more accurately. The volume of the daughter cells indicated a net loss of about one or two per cent in volume.

The parameter Q is roughly determined by the average slope of the constriction curve in the region of half constriction. If one uses this average to measure the constriction rate, one can say that there is probably a positive correlation between the rate of constriction and size.

Summary. It has been found that the constriction curves are predicted to a fair degree of approximation. From the analysis of the constriction curves it has been possible to predict the value of K independently of that from the elongation curves. In both cases the order of magnitude is the same, but the one set of values vary from about one-third to three times that of the other, without apparent correlation. Since the values of K from the constriction curves seem to vary with r_0 as predicted, whereas this is not so in the case of the elongation data, one would be inclined to accept the former values in any comparisons. If so, except for a possible slight effect of the KCl treatment, the only effect on K that is found is that of the size of the cell. The value of Q for the daughter cells is close to one-half of the value of Q from the original cell.

The author is indebted to Dr. N. Rashevsky for his many suggestions, and to Dr. R. Buchsbaum for his kindness in permitting the use of the photographs and records.

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TABLE OF PARAMETERS

Parameters	Normal	Shaken	KCl	KCN	Second Cleavage
Elongation Curves					
$A \text{ sec}^{-1}$	.025	.024	.020	.020	.025
$B \text{ sec}^{-1}$	.22	.059	.031	.048	.071
ε_m	.12	.40	.64	.44	.35
$\varepsilon'_m 10^{-3} \text{ sec}^{-1}$	.37	2.3	3.3	2.2	2.3
$t'_0 \text{ min}$	48.	46.	43.	57.	72.
$2r_0 10^{-4} \text{ cm}$	74.	69.5	71.	68.	58.
$K 10^{-3} \text{ cm sec}^{-1}$	1.7	.45	.26	.36	.45
$\gamma/\eta 10^{-3} \text{ cm sec}^{-1}$	2.1	.49	.24	.39	.5
Constriction Curves					
$Q 10^{-8} \text{ cm}^2 \text{ sec}^{-1}$	2.6	2.9	3.9	2.8	1.5
$r' \text{ cm}$	.013	.013	.015	.014	.012
$K 10^{-3} \text{ cm sec}^{-1}$	.62	.73	1.0	.72	.48

AN EXPRESSION FOR THE RATE OF RETURN OF AN EGG AFTER ARTIFICIAL DEFORMATION

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The forces which may be involved in the restoration of a deformed cell to its normal shape are considered. Estimates of the order of magnitude of the forces suggest that the most important forces are those due to surface tension, membrane elasticity and viscosity. An approximate expression is then derived for the rate of return of an elongated or compressed egg. The former expression is compared with data on eggs of *Arbacia* by E. N. Harvey and H. Shapiro, and it is found to agree sufficiently well with the data. The initial surface force is too low compared with that given by K. S. Cole but various factors are discussed which could contribute to this discrepancy. The value for the net viscosity of the egg is about twice the value arrived at by L. V. Heilbrunn for the egg protoplasm.

If a cell is deformed by an external force, various forces may tend to restore it to the normal shape. These may be grouped into surface forces and volume forces. The surface forces may be subdivided into surface tension, elastic membrane tension and osmotic forces. The former is independent of area, while the second is probably directly proportional to the change in area, at least over the initial range. The volume forces may be due to electrical or diffusion phenomena. The effect of electrical forces can probably be neglected (Rashevsky, 1938, Williamson, 1939). The same may be true for electrical surface forces. If the period for return to normal after deformation is short compared with the time constant, Λ , of diffusion processes (Landahl, 1939), we may consider the diffusion field as constant. For *Arbacia* eggs, Λ for oxygen is about four seconds, and that for other metabolites probably considerably greater. Then the effect of diffusion and osmotic forces will have little effect on the form of the curve of change of shape. As the eggs do not appreciably deform under the action of gravity, we shall neglect this volume force. Thus none of the volume forces will be considered.

Opposing the surface forces are those due to the inertia and the viscosity of the material of the egg itself, the latter being the resultant of the viscosity of the protoplasm including the effect of the granules, internal structure, and membrane, as well as the viscosity of the surrounding medium. The effect of this latter viscosity is roughly

to add to the net effect of the cell viscosity. This may be seen in the expression obtained by J. A. Wheeler for the "relaxation" time in the case of a true surface tension (Harvey and Shapiro, 1941). Since the effect of the cell is then at least several times that of the surrounding medium, the assumption of simple additivity introduces a negligible error. The inertial terms are not more than a fraction of a per cent of the term due to surface forces. They may be estimated as follows. At any instant the force due to inertia will not be of a greater order of magnitude than if the half mass were accelerated at the rate at which the pole is accelerated. This product of the half mass with the acceleration gives a force which may be compared with the effect of surface tension for that particular degree of elongation. An estimation indicates that the former is at most a fraction of a per cent of the latter. An assumption of an elastic membrane force only increases the effect at greater elongations and it is only for these shapes that the inertial effect is at all appreciable. Hence we shall not consider the effect of inertial terms.

Let $2r_1$ be the length and $2r_2$ the width of a deformed cell whose diameter in the spherical shape is $2r_0$. We shall assume that any deformations can be approximated by an ellipsoid of revolution about the z -axis, along which r_1 is measured. Let the surface force per cm. at any point be $\gamma'(x, y, z) = \gamma'(\rho, z)$, where $\rho^2 = x^2 + y^2$. If K_1 and K_2 are the principle curvatures at (ρ, z) and γ'_1 and γ'_2 are surface forces per cm. in the respective directions, then the normal component is $\gamma'_1 K_1 + \gamma'_2 K_2$. The component of γ' which is due to a surface tension is independent at deformation, and can be treated without too great difficulty. The component due to an elastic membrane tension is of a different order of complexity. For this reason, in order to treat the problem, we shall introduce an approximation and for the present only consider the deductions which then follow. We shall assume that the elasticity is the same in any direction, though, in general, it may not be isotropic. We shall introduce an average surface force γ which is the average value of $\gamma_1 + \gamma_2$ over the surface for a particular deformation. We shall further assume that γ varies approximately linearly with increase in area, or that

$$\gamma = \gamma_0 + \frac{\zeta \Delta S}{S_0}, \quad (1)$$

where S_0 should be taken as the surface of the sphere of no membrane tension, ΔS is the change in the surface and ζ is a constant. Without much error one can let $S_0 = 4\pi r_0^2$ and measure the area changes from this value. That the relation of (1) is then approximately lin-

ear in the case of *Arbacia* eggs is indicated by unpublished data furnished by Dr. K. S. Cole. The value of ζ is in this case about 0.58 dynes per cm. If one takes the value for the membrane tension .19 dynes per cm. given by Harvey (1931) for a twenty-five per cent increase in surface area and uses the value .08 for the initial value (Cole, 1932) one obtains $\zeta = 0.44$ dynes per cm., a value which agrees rather well with that above.

It may be pointed out in this connection that the surface force measured by Cole (1932) by the compression method is a quantity of the same type of average as γ used here. Evidently when the shape is only infinitesimally different from a sphere the error in γ is negligible. But for large deformations the error introduced may become considerable.

The relative rate of change of the half length, r_1 , under the influence of surface forces only, is given by Betti's theorem applied to plastic flow by the equation

$$\frac{1}{r_1} \frac{dr_1}{dt} = \frac{1}{3\eta V} \iint [zZ - \frac{1}{2}(xX + yY)] dS, \quad (2)$$

where V is the volume of the cell, η is the viscosity, X , Y and Z are the components of the surface forces along the x , y and z axes. The integration has been carried out by G. Young (1939) for the case in which the cell is a prolate ellipsoid of revolution. The result is [Young, 1939, equation (72)]

$$\frac{1}{r_1} \frac{dr_1}{dt} = -.53\beta \frac{\gamma}{\eta} \frac{(r_1 - r_2)}{r_1 r_2}, \quad (3)$$

where $\beta = 1$ for $r_1 = r_2$, $\beta = .94$ for $r_1 = 2r_2$ and $\beta = .74$ for $r_1 \gg r_2$. We shall be interested in a range $r_1 = r_2$ to $r_1 \infty 2r_2$ so that we may set $\beta = 1$ without appreciable error. A consideration of the case of the oblate ellipsoid shows that equation (3) again holds, but β takes on slightly different values. Considering constant volume so that

$$r_1 r_2^2 = r_0^3, \quad (4)$$

and setting

$$\varepsilon = \frac{r_1 - r_0}{r_0}, \quad (5)$$

we may write equation (3) in the form

$$\frac{d\varepsilon}{dt} = \frac{-.53\gamma}{\eta r_0} [(1 + \varepsilon)^{3/2} - 1]. \quad (6)$$

In order to integrate equation (6), it is first necessary to obtain the relation between γ and ε . This follows directly when we find the relation between $\Delta S/S_0$ and ε . Substituting the value of the area of a prolate ellipsoid of revolution into $(S - S_0)/S_0$ and using equations (4) and (5) we have an expression for $\Delta S/S_0$ in terms of ε . Evaluating the square root of $\Delta S/S_0$ numerically for values of ε and plotting the result one finds an approximately straight line relationship in the range $\varepsilon = 0$ to $\varepsilon = 0.6$. Deviation becomes marked beyond this, the function being concave downwards. For the oblate ellipsoid, the curve becomes markedly concave upwards beyond about $\varepsilon = -0.4$. In the range of ε from -0.3 to 0.6 we may write

$$\frac{\Delta S}{S_0} = 0.4 \varepsilon^2 (1 - 0.8\varepsilon + \dots), \quad (7)$$

where the error is about twenty per cent at the extremes. The range in $d\varepsilon/dt$ which we wish to consider is found experimentally to vary by a factor of the order of a hundred in the range of from 0.1 to 0.6 . Thus a considerable error in $d\varepsilon/dt$ at any point can be tolerated.

Introducing equation (7) into (1) and the resulting equation into (6) we obtain,

$$\frac{d\varepsilon}{dt} = -\frac{.80}{\eta r_0} (\gamma_0 + 0.4 \zeta \varepsilon^2) \varepsilon, \quad (8)$$

where we neglect the factor $(1 + \varepsilon/4 - \varepsilon^2/24 + \dots)$ from the expansion of the brackets in equation (6), as well as the factor $(1 - 0.8\varepsilon + \dots)$ of equation (7). The error in neglecting the first factor is not more than fifteen per cent, while that of the second factor may be about fifty per cent at $\varepsilon = 0.7$, but in the opposite direction. It is equivalent to requiring that 0.4ζ is larger than $\gamma_0(6/\varepsilon - 1)/24$. Since we shall not consider values of ε less than about 0.05 , this amounts to requiring that γ_0 should be less than about 0.05 .

Integrating equation (8) and setting $\varepsilon = \varepsilon_0$ for $t = 0$, we obtain

$$t = \frac{.63 \eta r_0}{\gamma_0} \log \frac{\varepsilon_0^2 (\gamma_0 + .4 \zeta \varepsilon^2)}{\varepsilon^2 (\gamma_0 + .4 \zeta \varepsilon_0^2)}. \quad (9)$$

The above expression might be expected to apply approximately for the recovery of a cell which had been compressed between two parallel planes and then released, as well as to the case in which a cell was elongated as a figure of revolution and then released. The necessity to assume an averaged γ in the integration presents itself as a difficulty. The error involved may not in general be the same for the prolate and oblate ellipsoids. Thus, to that extent, agreement be-

tween corresponding parameters obtained from the two procedures would tend to justify the approximate treatment used. One would allow a slight overestimation of perhaps twenty per cent in one case and a corresponding underestimation in the other due to the fact that the errors in equation (8) are in the opposite direction.

It may at times be convenient to use the ratio of the length to the width as a measure. If this is designated by R , one may substitute for ε the value $\varepsilon = R^{2/3} - 1$ in equation (9) and obtain an expression for the ratio of length to width as a function of time.

We shall now compare the relationship described by equation (9) with the experimental results obtained by E. N. Harvey and H. Shapiro (1941) from *Arbacia* eggs returning to normal after having been passed through sufficiently small capillaries to elongate them. From the length of the cell, r_1 , at any instant, the value of ε can be obtained by equation (5), so that an empirical $\varepsilon(t)$ relation is obtained. Comparing equation (9) with this relationship, one can determine the parameters. The $\varepsilon(t)$ relation is thus determined, and because of equation (4) and the condition for constant volume, $r_1(t)$ and $r_2(t)$ are determined.

In comparing equation (9) with the empirical relation, it is found that the value of γ_0 is required to be less than about 0.01, (and greater than about -.002) or the empirical relation does not even approximately agree with the theoretical. Within this range the ratio of the parameters η/γ_0 to ζ/γ_0 is nearly constant and approximately the same as that obtained when γ_0 is taken equal to zero, for which $\eta/\zeta = 0.36$ cm. sec.⁻¹. Hence, we shall use $\varepsilon(t)$ as if $\gamma_0 = 0$, though only requiring that it should not be larger than about 0.01. This restriction is sufficient to satisfy the previous condition that γ be less than 0.05. Instead of equation (9) we then obtain the equation

$$\varepsilon = \sqrt{\frac{\eta r_0 \varepsilon_0^2}{\eta r_0 + .64 \zeta \varepsilon_0^2 t}} \quad (10)$$

Introducing this expression for ε into (4) and (5) we obtain $r_1(t)$ and $r_2(t)$. Since it is the length, $2r_1$, and width $2r_2$, which are measured, we write

$$2r_1 = 2r_0 [1 + \{\varepsilon_0^2 / (1 + .64 \zeta \varepsilon_0^2 t / \eta r_0)\}^3], \quad (11)$$

$$2r_2 = 2r_0 [1 + \{\varepsilon_0^2 / (1 + .64 \zeta \varepsilon_0^2 t / \eta r_0)\}^3]^{-1}. \quad (12)$$

When $\eta/\zeta = 0.36$, $\varepsilon_0 = 0.72$ and $2r_0 = 76 \times 10^{-4}$ cm., we obtain the curves shown in Figure 1. Using the value $\zeta = 0.58$ given above, we then obtain $\eta = 0.21$ poise. To obtain the net viscosity of the egg,

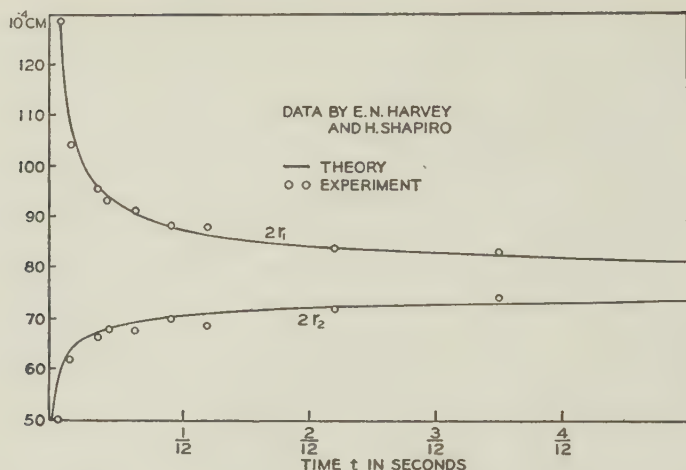


FIGURE 1

one should subtract approximately .01 because of the surrounding medium and perhaps allow for overestimation as mentioned above, giving $\eta_e = 0.16$ poise. The value η_e should be the total effective viscosity of the egg as a whole, if one could rely upon the approximations made. According to Heilbrunn, (1928), the viscosity of the fluid portion of the *Arbacia* egg is about .03 poise, while the viscosity uncorrected for granules is about 0.07 poise. The presence of larger structures may contribute appreciably to the total effective viscosity. Just to what extent this may be, would require a more detailed analysis. There is also the possible effect of the various membrane layers which affect the net viscosity. If we could assume that the value of $\eta_e = 0.16$ is correct, then we should conclude that the contribution to η_e by structures and membranes would be an amount approximately equal to that due to the protoplasm with granules. This would not imply that the amount contributed by the membrane gives its viscosity, though it may be possible to estimate it. In any case the value of η_e obtained is sufficiently plausible as to the order of magnitude. Using the value of ζ from the data by E. N. Harvey given above, we obtain $\eta_e = 0.11$ poise.

If the external viscosity instead of being that of water were increased by a factor of 15, the above estimates would predict that the constant of the curve, η/ζ , would be about doubled. Conversely one could thus determine the effective viscosity of the egg approximately as that value of the external viscosity which just doubles the constant η/ζ .

Thus far we have only required that γ_0 be of the order or less

than about 0.01 dynes per cm. The value for summer eggs, as measured by K. S. Cole (1932), is 0.08 dynes per cm. Only one-half this value is obtained for late summer eggs (Cole and Michaelis, 1932). In the experiments under discussion, late season eggs were used. This is still probably too large a discrepancy to overlook, so we seek some explanation. Until the more exact solution to the problem, as mentioned above, is given, one cannot exclude the possibility that there would be no disagreement if the complete solution were known.

Since equations (11) and (12) represent the data, we can say that the rate of change of ε is approximately proportional to ε^3 . If a true surface tension is assumed, we see from equation (6) that the rate is approximately proportional to ε . The approximation made initially, of an average effective γ , probably has the effect of increasing the restoring force for large elongations. Also as the shapes diverge from the elliptical shape in the direction of a truncated cylinder, the effect of elongation is perhaps appreciably accentuated. That the shape is not quite elliptical is seen from Figure 1, where the measured widths are somewhat lower than that expected, although the lengths are about correct.

The naked surface of *Arbacia* eggs is apparently liquid, as indicated by experiments on coalescence (Chambers and Kopac, 1937). The outer layers are more solid in nature (Chambers, 1940; Kopac, 1940). However, it is likely that a certain amount of plastic flow may take place in the surface. This results in a hysteresis phenomena as is observed in protein membranes (Harvey, 1936). This property would tend to reduce γ_0 to some extent. But it is likely that the measured value used above includes such an effect. Another factor not taken into account is the possible effect of volume elasticity (Pfeiffer, 1937). However, E. Howard (1931) finds no evidence of plastic flow in *Arbacia* protoplasm over a considerable range of temperature. These observations did not include the firmer layers in the region of the surface. In general, if any part of the protoplasm has an effective finite yield point, the stable shape after a deformation beyond this point would deviate from spherical depending on the value of the elastic coefficient and the yield point. There is insufficient data at present to make an estimate of such a possible effect.

As was mentioned previously, the time constants for the diffusion processes are probably well below the relaxation period. However, the initial disturbance in the diffusion fields, due to the deformation of the cell as well as to the presence of the deforming mechanism, might result in a force which tends to keep the cell slightly deformed. Thus the cell might approach a shape which is not a sphere (House-

holder, 1941). The latter shape would reduce to a sphere at a rate depending upon the time constants, Δ , of the metabolites.

In view of the above factors, one cannot rely on the estimated value of η_e as given above, but its order of magnitude may well be correct. At least it is not necessary to assume such a large value as is indicated by the analysis on the basis of a surface tension (Harvey and Shapiro, 1941).

The data on *Chaetopterus* eggs given by E. N. Harvey and H. Shapiro do not cover a sufficient range to determine a permissible range for γ_0 . However, if we neglect its effect and use equation (10), together with the relation $\varepsilon = R^{2/3} - 1$, the data in the range given lie close to the theoretical curve for which η/ζ is about fifty. The surface forces for *Chaetopterus* eggs are quite comparable as to order of magnitude with *Arbacia* (Harvey, 1931). If ζ should have the same value in each case, the viscosity in this case would be about one hundred and fifty times that for *Arbacia* eggs.

Summary. An expression for the length and width of a cell, which has been given an initial deformation, as a function of time is derived by an approximate method on the assumption that the surface of the cell may be elastic. The expression is found to agree with data from *Arbacia* eggs but the value of the initial surface force is not more than about one-third of that obtained by fairly direct measurements. Some of the factors that may be responsible for the discrepancy in the initial surface force are discussed. The value of the viscosity thus estimated is of the order of that of the fluid part of the egg as determined experimentally.

The author is indebted to Dr. N. Rashevsky and Dr. A. S. Householder for reading and discussing the manuscript.

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AN ANALYSIS OF THE SHAPES OF A CELL DURING DIVISION WITH PARTICULAR REFERENCE TO THE ROLE OF SURFACE TENSION

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An expression is given for the contribution to the relative elongation by any volume element or its surface. The case in which only a constant surface tension is acting is considered in greater detail. From measurements of an egg in several stages, the empirical variation of an expression proportional to the above function is obtained. In the constricting region and near the ends of the cells, the change of shape is opposite to that which would be due to a constant surface tension alone. The effect of streaming which may arise from a variable surface tension is considered. The effect of forces which arise in this manner may be sufficient to explain the discrepancy in the constricting region if the streaming is considered due largely to such a variable surface tension.

The shape of a cell at any instant, as well as changes of shape with time, can be considered as the resultant of various volume and surface forces. If the former can be derived from a potential, one may substitute for them an equivalent surface force. The average relative change in length of the cell can be written as (Rashevsky, 1940)

$$\bar{e} = \frac{1}{r_1} \frac{dr_1}{dt} = \frac{1}{3\eta V} \iint [zZ - \frac{1}{2}(xX + yY)] dS, \quad (1)$$

where $2r_1$ is the length, η is the viscosity, V the volume of the cell, X , Y and Z are the components of the total surface force given by the sum of the surface forces and the surface force equivalent of the volume forces. If we consider a figure of revolution about the z -axis, let $\rho^2 = x^2 + y^2$ and let ν be the normal to the surface at (ρ, z) , then equation (1) may be written, on integrating with respect to the polar angle,

$$\frac{\delta \bar{e}}{\delta z} = \frac{2\pi}{3\eta V} \rho (zZ - \frac{1}{2}\rho P) \sec(\nu\rho), \quad (2)$$

where P is the component of the total surface force along the ρ -axis.

The left hand member of (2) represents the contribution to average relative elongation $\bar{e}$, by the surface of the element between z and $z + \delta z$. Its value can be measured for any z at a particular time, so that $Z(P)$ could be determined. This gives little information about

Z and P , which themselves are composite surface force components. We shall instead consider the component of $\delta\bar{e}/\delta z$ is due to a surface tension, γ , which has a constant value over the surface. If R_1 and R_2 are the principle radii of curvature and R twice their harmonic average, then that part of $\delta\bar{e}/\delta z$ due to this factor may be written

$$\frac{\delta\bar{e}}{\delta z} = -\frac{2\pi\gamma}{3\eta V} \frac{\rho}{R} [z \tan(\nu\rho) - \tfrac{1}{2}\rho] = \frac{2\pi\gamma}{3\eta V} \phi(z), \quad (3)$$

where $\phi(z)$ is defined by this equation and is a function of z since the shape determines $\rho(z)$. The function $\phi(z)$ can be determined empirically for any given shape by measuring ρ , R_1 , R_2 and $\tan(\nu\rho)$ for any z . The empirical expression for $\phi(z)$ may give some insight into the role played by surface tension. For this reason, enlarged photographs of three successive stages of an *Arbacia* egg, denuded by treatment with *KCl*, were measured to determine $\phi(z)$ as shown in Figure 1. The photographs were obtained through the courtesy of Dr. R. Buchsbaum. Each point is obtained from measurements of the egg. The curves correspond to the tracing of the shapes correspondingly numbered in the figure. The time between stages is half a minute. The curves, which are free hand drawings through the points, are stopped at the end point of the cell along the elongation axis. The value of ϕ at the end of the cell is obtained from measurements and the limit of $\rho \tan(\nu\rho)$ is obtained analytically by assuming that the end is approximated by part of a sphere. The area under the positive part of each curve is very nearly equal to the total area under the negative parts. From the curves, we see that the effect of a true surface tension for these shapes is such that in the region of the neck the tendency is to reduce elongation, and thus to reduce constriction. The effect becomes progressively greater with time. Evidently some other surface or volume force than a surface tension must be acting here to cause constriction. In the middle range, from about $.5 \times 10^{-3}$ to 3×10^{-3} cm., the effect of surface tension is such as to produce an elongation. This effect, as measured by the area under the positive part of the curves, is much the same in successive shapes, perhaps decreasing with time. If so, the change in shape in this region is as expected from a surface tension. The part of the curve near the end shows the existence of a tendency to reduce elongation. A comparison of the areas under the curves indicates that the tendency to oppose elongation becomes greater with succeeding shapes. Thus the shape in this region is changing in the wrong way from that expected by a surface tension. Thus it is probable that the effect of volume forces and surface forces, other than that due to a constant surface tension, must be such that, in the neck

region and near the ends, the contribution towards elongation will be positive.

The variation of surface tension from pole to equator has been suggested as a factor in cell division (Spek, 1918, cf. also Wilson, 1925). It should be noted that a variation of the surface tension with z would not greatly affect the above argument as such variations of force could be sustained by the outside medium. However, this is perhaps not probable. It is more likely that variations of surface tension would be sustained largely by streamings set up in the cell. In general, such streamings are observed. One might attempt to compute the magnitude of the velocity of the streaming necessary to sustain the variations required to make the net elongation positive, or, using the observed order of magnitude of such streamings, to obtain the effective volume force in the neck region and see whether this could overbalance the negative effect of surface tension.

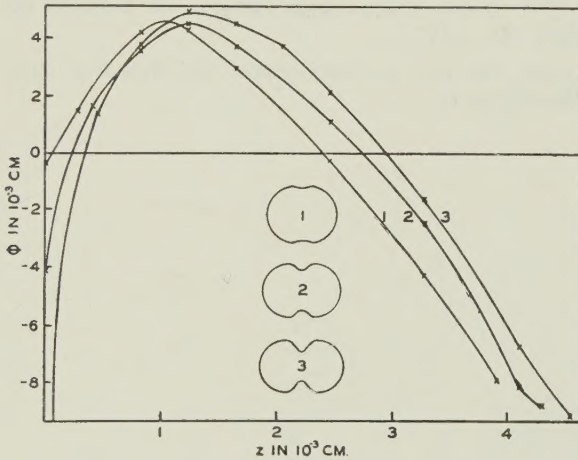


FIGURE 1

Consider the case of the shape II of Figure 1. The average of ϕ in the neck region in which $\phi < 0$ is $\bar{\phi} = -1.4 \times 10^{-3}$ cm. If we use $\gamma \sim 10^{-1}$ dynes cm^{-1} , the average value of $\delta\bar{e}/\delta z$, in this region, due to surface tension is $-.5/\eta$ sec^{-1} . The contribution to $\delta\bar{e}/\delta z$ for this region due to streaming, which we assume to be due only to the variable surface tension, may be estimated in the following manner. If the velocity of streaming in this region, is assumed to be $\sim 10^{-3}$ cm. sec^{-1} , falls off to a negligible value in a distance, $d \sim 3 \times 10^{-4}$ cm., or about one-half the width of the neck, so that $d = z$ for $\phi = 0$, then the force per unit area is $\eta v/d$. The area upon which this is acting is of the or-

der of πr^2 , where r is the radius of the neck. This force is equivalent, in order of magnitude, to a pressure on the surface of the neck, in the region where $\phi < 0$, of $\pi r^2 \eta v / (d\pi r d)$. Dividing this pressure by 3η we obtain for the contribution to $\delta\bar{e}/\delta z$ in this region due to the streaming, the value $rv/(3d^2) \approx 10 \text{ sec.}^{-1}$. We have considered the pressure to be of the order of magnitude, of the pressure difference. Comparing this value with that for surface tension alone, and giving η a value of 10^{-1} poise, we see that the latter could be an important factor at this particular stage. In this illustration we may have underestimated the former and overestimated the latter. It may be noted that the effect of the viscosity does not enter the resulting expression for the contribution to the relative elongation rate due to streaming.

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